sciendo

106 ENDOCRINE REGULATIONS, Vol. 57, 106–113, 2023

doi:10.2478/enr-2023-0013

Comparison of aspartate aminotransferase platelet ratio index score and insulin resistance in type 2 diabetes mellitus with non-alcoholic fatty liver disease

Nikhil Gupta, Waseem Ramzaan Dar, Asma Wani, Rachit Raj Saxena, Sahil Khatri, Bhumesh Tyagi, Pankaj Bansal, Irfan Ahmad Mir

Department of Medicine, School of Medical Science & Research, Sharda University, UP, India
E-mail: dr.irfan765742@gmail.com

Objective. Nonalcoholic fatty liver disease (NAFLD) is a spectrum of liver diseases characterized by the presence of ectopic fat in the liver and steatosis, which cannot be explained by alcohol consumption. The association between NAFLD and type 2 diabetes mellitus (T2DM) is well established. As liver fibrosis progresses in a patient with NAFLD, insulin resistance (IR) increases and may worsen diabetes control. The aspartate aminotransferase platelet ratio index (APRI) score is a simple and inexpensive bedside marker that can detect liver fibrosis and cirrhosis. Several studies have shown an association between APRI and NAFLD. However, there is a gap in correlation with IR in patients with diabetes. In this study, we sought to correlate IR and NAFLD in diabetes using the APRI score.

Methods. This observational hospital-based cross-sectional study was conducted in the Department of General Medicine, one of the tertiary care hospitals in North India, from February 2019 to July 2020. A total of 70 patients were taken for the study. Patients with T2DM, aged >30 years, who had no history of alcohol use and who had or were newly diagnosed with NAFLD were enrolled in the study.

Results. Significant differences in mean HbAc1, AST, serum insulin, APRI score and homeostatic model assessment-2 (HOMA2) IR between NAFLD grade 1, grade 2, and grade 3 groups were found. Pearson correlation between APRI score and HOMA2 IR total values revealed a significant positive correlation between them.

Conclusions. The data of the present study indicate that the APRI score can be used to assess the IR degree and provide important information for improving glycemic control in T2DM patients with NAFLD.

Key words: APRI, insulin resistance, type 2 diabetes mellitus, nonalcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD) is a spectrum of liver diseases characterized by the presence of ectopic fat in the liver and steatosis, which cannot be explained by alcohol consumption (Machado and Cortez-Pinto 2014). NAFLD is now recognized as one of the most important chronic liver diseases in developed countries (Suzuki et al. 2005). The association between NAFLD and type 2 diabetes mellitus (T2DM) is well established, which could be explained by insulin resistance (IR) and compensatory hyperinsulinemia leading to impaired lipid metabolism and accumulation of hepatic triglycerides (TG) in NAFLD or β-cell dysfunction in T2DM (Forlani et al. 2016). The clinical associations of NAFLD with the elements of metabolic syndrome, including obesity, hypertension, and dyslipidemia,

Corresponding author: Dr. Irfan Ahmad Mir, Assistant Professor, Department of Medicine, School of Medical Science & Research, Sharda University, UP, India 201306; e-mail: dr.irfan765742@gmail.com.

are also well-established (Kalra et al. 2013). T2DM is a multifactorial disease, in which the body no longer responds properly to physiological insulin concentrations, usually due to chronic overeating and obesity. Hepatic IR appears to be an important underlying mechanism of NAFLD along with chronic dyslipidemia (Smith and Adams 2011). Epidemiological studies have shown that 18% to 33% of individuals with NAFLD also have T2DM and as many as 66% to 83% of individuals with fatty liver disease have a dim of IR (Browning et al. 2004; Jimba et al. 2005; Lopez-Velazquez et al. 2014). Fatty liver or steatosis is said to occur when more than 5% of hepatocytes in a liver biopsy show ectopic lipid droplets (Ratziu et al. 2010). Recently, experts agree that NAFLD does not reflect current knowledge and propose metabolic (dysfunction) associated fatty liver disease (MAFLD) as a more appropriate term. The new definition places greater emphasis on the important role of metabolic dysfunction (Xian et al. 2020). NAFLD is associated not only with hepatic morbidity and mortality but also with increased cardiovascular risk. NAFLD and cardiovascular disease share several risk factors, such as obesity, metabolic syndrome, hypertension, dyslipidemia, T2DM, and chronic kidney disease (Muzurovic et al. 2021, 2022).

The gold standard for diagnosis is liver biopsy, especially for the diagnosis of nonalcoholic steatohepatitis (NASH) and staging of fibrosis. Liver biopsy cannot be used routinely because it is an invasive and expensive procedure, prone to sampling errors, captures only an insignificant volume of the liver, and represents a disease, in which lesions are unevenly distributed throughout the liver, leading to the false exclusion of NASH and misclassification of the degree of fibrosis in a quarter of cases (Merriman et al. 2006). On the other hand, it is highly dependent on the pathologist, especially in the diagnosis of NASH. In recent years, an index composed of routinely available laboratory tests, namely the aspartate aminotransferase to platelet ratio index (APRI) (Wai et al. 2003; Shah et al. 2017) has been developed for the evaluation of liver fibrosis in patients with chronic hepatitis B and C. This index is used to assess the degree of fibrosis.

It is well documented that both NAFLD and diabetes mellitus (DM) are interrelated and have a bidirectional relationship. IR is an important risk factor that applies to both NAFLD and DM. As liver fibrosis progresses in a patient with NAFLD, IR increases and may worsen diabetes control. The APRI score is a simple, inexpensive bedside marker that can detect liver fibrosis and cirrhosis. Several studies have shown an association between APRI and NAFLD (Kruger et al. 2011; Lee et al. 2021). However, there is a gap in correlation with IR in patients with DM. In addition, it needs to be clarified whether APRI correlates with different grades of NAFLD and whether it can be used to support the association between NAFLD and IR in T2DM. In this study, we sought to correlate IR and NAFLD in diabetes using the APRI score.

Material and Methods

Subjects. This cross-sectional hospital-based study was conducted in the Department of General Medicine, one of the tertiary care hospitals in North India, from February 2019 to July 2020. The research procedure used was in accordance with the approved ethical standards of the institution under notification number SU /SMS&R/76-A/2019/61.

A total of 70 patients who attended an Outpatient Department (OPD) and/or were admitted for study purposes, gave written consent, and met the inclusion criteria were recruited for this study. The selection of patients followed these inclusion and exclusion criteria. Inclusion criteria: 1) all patients of T2DM aged >30 years; 2) no history of alcohol intake; and 3) history of or newly diagnosed NAFLD. Exclusion criteria: 1) patients in any stage of pregnancy; 2) patients with hepatitis B or hepatitis C; 3) patients with a history of any liver disease, apart from NAFLD or any haematological disorder; 4) patients with a history of repeated blood transfusions; 5) patients of thrombocytosis or thrombocytopenia; 6) patients admitted or with a history of any acute illness in the last 4 weeks; 7) patients with autoimmune disorders; 8) patients with a history of use of hepatotoxic drugs. A total of 85 patients were screened, 8 declined to participate in the study, and 7 did not meet the inclusion criteria. Finally, 70 patients with NAFLD and T2DM were found eligible according to the inclusion criteria. After written informed consent was obtained, a detailed history of the presenting symptoms and their occurrence was taken. A detailed history was obtained from all patients, and demographic information, patient's age, clinical details, blood pressure, heart rate, and body mass index (BMI) were noted on the patient's proforma. Ultrasonography, fasting blood glucose and HbA1C determination, ELISA for fasting insulin level and homeostatic model assessment-2 (HOMA2) software, liver function test (LFT) and complete blood count (CBC) for APRI score calculation were also performed.

Patients were diagnosed as diabetic according to the latest American Diabetes Association guidelines (American Diabetes Association 2020).

NAFLD degree and APRI score. Patients were also diagnosed as having NAFLD on the basis of undergoing a sonographic scan and the degree of NAFLD was recorded. When the echogenicity is just increased, it is a grade I; when the echogenic liver obscures the echogenic walls of portal vein branches, it is grade II, and, when the echogenic liver obscures the diaphragmatic outline, it is grade III fatty infiltration (Saadeh et al. 2002). APRI score was calculated using the following formula (Lin et al. 2011):

APRI = (AST in IU/L) / (AST Upper Limit of Normal in IU/L) / (platelets in 10^9/L).

Based on a meta-analysis by Lin et al. (2011), for significant fibrosis, an APRI threshold of 0.7 was 77% sensitive and 72% specific; for severe fibrosis, a threshold of 1.0 was 61% sensitive and 64% specific; and for cirrhosis, a threshold of 1.0 was 76% sensitive and 72% specific.

Biochemical parameters. Six ml of fasting (8–12 h) venous blood samples were taken from all subjects participating in the study and divided into 3 parts: the 1st part was put in a plain tube and left to clot and the blood was centrifuged at 3000xg for 15 min. The plasma was then stored at –20 °C for the determination of serum insulin levels. Fasting serum insulin levels were measured using an EDI™ Human Insulin ELISA kit in 70 selected sera. The assay utilizes the "sandwich" technique with selected antibodies that bind to various epitopes of insulin. Intra- and inter-assay coefficient of variations (CVs) were 7.8 and 9.4% for insulin, respectively.

The 2nd part of the blood sample was put in a tube containing EDTA and transferred to the Central Laboratory of the hospital for determination of fasting blood glucose, HbA1C and platelet count. Fasting blood glucose was measured by the GOD-POD method. HbA1c was measured using an autoanalyzer. Platelet count was obtained by hydrodynamic focusing on automated Sysmex XT1800i.

The 3rd part of the blood sample was put in a plain tube and left to clot. The serum was then separated using a centrifuge at 3000xg for 15 min. The serum was then used to measure the AST levels by kinetic with pyridoxal 5 phos-on VITROS FS 5.1, respectively.

Once the data were collected for all the patients, the HOMA2 calculator was provided by the University of Oxford, diabetes trial unit. Calculation of %B (a measure of β-cell activity), %S (insulin sensitivity), and IR by inputting the fasting blood glucose and fasting serum insulin values was performed on the calculator of Oxford University.

Statistical analysis. Microsoft Excel was used in creating the database and producing graphs, while the data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 23.0 for Windows. Mean and standard deviation (SD) were used to describe quantitative data meeting normal distribution. Continuous two independent groups were compared by parametric independent Student's t-test. ANOVA (one way) was used to perform intergroup analysis involving more than two groups. The Pearson coefficient was calculated to evaluate the correlation between two sets of data. A p-value less than 0.05 ($p<0.05$) was considered statistically significant.

Results

Of the 70 patients recruited for this study, 38 were male (54.3%) and 32 were female (45.7%). The subjects were divided on the basis of NAFLD grades as ascertained on ultrasonography. There were 30 patients with grade 1 (42.85%), 30 patients with grade 2 (42.85%) and 10 patients with grade 3 (14.30%) NAFLD.

The mean age of subjects in the grade 1, grade 2 and grade 3 NAFLD groups was 46.60±13.56, 42.37±10.92 and 47.80±2.49 years, respectively. There was no statistically significant difference in age between these groups ($F=1.375$; $p=0.260$) (Table 1).

The mean BMI for NAFLD grade 1, grade 2 and grade 3 groups was 28.78±3.24, 28.23±2.68 and 29.18±1.14 kg/m^2, respectively. No statistically significant difference in mean BMI between grade 1, 2 and 3 NAFLD groups ($F=0.546$; $p=0.582$) was found (Table 1); however, patients in all three groups were overweight. No significant difference was found for the intergroup comparisons in mean BMI between NAFLD grade 1, 2 and 3 groups using the post-hoc Bonferroni test (Table 2).

The mean HbA1c values in grade 1, 2, and 3 NAFLD groups were 7.086±0.675, 7.583±0.988 and 10.69±2.261%, respectively. There was a significant difference in mean HbA1C between NAFLD grade 1, 2 and 3 groups ($F=36.0608$; $p<0.001$) (Table 1). The mean HbA1C was significantly higher in NAFLD grade 3 group compared to grades 1 and 2 NAFLD groups (both $p<0.001$) (Table 2).

The mean AST levels in grade 1, 2, and 3 NAFLD groups were 43.22+16.93, 60.94+23.37 and 86.36±26.21 (IU/L), respectively. Our study showed that there was a significant difference in mean AST

Table 1
Characteristics of patients according to grades of NAFLD

Parameter	NAFLD grade			F	p-value
	Grade 1	Grade 2	Grade 3		
No. of patients	30 (42.85%)	30 (42.85%)	10 (14.30%)		
Age (years)	46.60±13.56	42.37±10.92	47.80±2.49	1.375	0.260
BMI (kg/m^2)	28.78±3.24	28.23±2.68	29.18±1.14	0.546	0.582
HbA1c (%)	7.086±0.657	7.583±0.988	10.690±2.261	36.608	<0.001
AST (IU/L)	43.22±16.93	60.94±23.37	86.36±26.21	16.310	<0.001
Platelet count (per microliter)	258,033±58,240	273,566±65,921	226,900±56,779	2.193	0.119
Serum insulin (IU/ml)	8.85±3.19	11.69±3.95	19.9±6.36	27.500	<0.001
APRI	0.426±0.201	0.566±0.198	0.990±0.321	24.501	<0.001
HOMA2-IR	2.84	8.21	-11.05		<0.001

Abbreviations: APRI – aspartate aminotransferase platelet ratio index; BMI - body mass index; HOMA2 – Homeostatic Model Assessment; IR – insulin resistance; NAFLD – nonalcoholic fatty liver disease; SD - standard deviation. Data are presented as mean±SD. One-way ANOVA test was used for statistical analysis. Values p<0.05 were considered statistically significant.

Table 2
Inter-group comparison of characteristics of patients and grades of NAFLD

Parameter	NAFLD	NAFLD grade 1 (difference)	p-value	NAFLD grade 2 (difference)	p-value
BMI (kg/m^2)	Grade 2	0.55	1.000	–	–
	Grade 3	–0.40	1.000	–0.95	1.000
HbA1c (%)	Grade 2	0.496	0.025	–	–
	Grade 3	–3.603	<0.001	3.106	<0.001
AST (IU/L)	Grade 2	17.72	0.001	–	–
	Grade 3	–43.14	<0.001	25.42	0.006
Platelet count (per microliter)	Grade 2	15.533	0.337	–	–
	Grade 3	31.133	0.149	–46.666	0.052
Serum insulin (IU/ml)	Grade 2	2.84	0.003	–	–
	Grade 3	–11.05	<0.001	8.21	<0.001
APRI	Grade 2	0.14	0.008	–	–
	Grade 3	–0.56	<0.001	0.42	<0.001
HOMA2-IR	Grade 2	0.430	0.003	–	–
	Grade 3	–1.841	<0.001	1.410	<0.001

Abbreviations: APRI – aspartate aminotransferase platelet ratio index; BMI - body mass index; HOMA2 – Homeostatic Model Assessment; IR – insulin resistance; NAFLD – nonalcoholic fatty liver disease; SD - standard deviation. Post-hoc Bonferoni test was used for statistical analysis. Values p<0.05 were considered statistically significant.

levels between NAFLD grade 1, grade 2 and grade 3 groups (F=16.310; p<0.001) (Table 1). The intergroup analysis demonstrated that the mean AST levels were significantly increased in the NAFLD grade 3 group compared to grades 1 and 2 groups (p<0.001 and p=0.006, respectively) (Table 2). The AST values in NAFLD group 2 were also significantly elevated compared to the grade 1 NAFLD group (p=0.001) (Table 2).

The mean platelet count was 258,033±58,240; 273,566±65,921 and 226,900±56,779 (per microliter of blood) in NAFLD grade 1, grade 2 and grade 3 groups, respectively. There was no significant difference in mean platelet count between NAFLD grade 1, 2 and 3 groups (F=2.193; p<0.119) (Table1). However, an increase in the platelet count in patients with grade 2 NAFLD when compared to the grade 1 NAFLD group and a decrease in platelet count in

the grade 3 NAFLD group when compared to grades 1 and 2 groups were found (Table 1). The intergroup comparison of mean platelet count using the post-hoc Bonferroni test showed no significant difference among NAFLD grades 1, 2 and 3 groups (Table 2).

In our study, the mean serum insulin levels were 8.85±3.19, 11.69±3.95 and 19.9±6.36 IU/ml in grades 1, 2 and 3 NAFLD groups, respectively. We found a significant difference in mean serum insulin levels between NAFLD grade 1, grade 2 and grade 3 groups ($F=27.500$; $p<0.001$) (Table 1). The intergroup comparison revealed that the mean serum insulin levels in NAFLD grades 2 and 3 groups were significantly increased when compared to grade 1 ($p=0.003$ and $p<0.001$, respectively) (Table 2).

The mean APRI score was 0.426±0.201, 0.566±0.198 and 0.990±0.321 in NAFLD grade 1, grade 2 and grade 3 groups, respectively. There was a significant difference in APRI score between NAFLD grade 1, 2 and 3 ($F=24.501$; $p<0.001$) (Table 1). The intergroup comparison of mean APRI score revealed a significant increase in NAFLD grade 3 compared to grades 1 and 2 ($p<0.001$) (Table 2).

The values of HOMA2 IR for grades 1, 2 and 3 of NAFLD were 1.233±0.475, 1.663±0.621 and 3.074±1.095, respectively. There was a significant difference in mean HOMA2 IR between NAFLD grade 1, grade 2 and grade 3 ($p<0.001$) (Table 1, 2).

As shown in Table 3, we applied Pearson's correlation to the overall values of APRI score and HOMA2 IR and found a significant positive correlation between them ($t=0.9727$; $p<0.001$). When the Pearson's correlation was applied to APRI score of individual grades of NAFLD and HOMA2 IR, we found a similar strong correlation between them. The correlation between APRI score and HOMA2 IR was 0.9628, 0.9443 and 0.9869 for grade 1, 2 and 3, respectively ($p<0.001$ for all grades) (Table 3).

Discussion

To the best of our knowledge, our study may be the first of its kind to investigate the association between APRI score and IR, as no studies have been conducted to date to find this association in T2DM patients with NAFLD. In our study, there were 30 patients (42.9%) with grade 1 NAFLD, 30 patients (42.9%) with grade 2 and 10 patients (14.3%) with grade 3. There was no statistically significant difference in age and BMI between these groups, but patients in all groups were overweight.

Our results showed that there was a significant difference in mean AST levels between NAFLD grade 1, 2 and 3 groups, the highest AST levels were in grade 3 NAFLD group. Ghamar-Chehreh et al. (2012) have revealed a significant direct relationship between ultrasonographic grading of the NAFLD and AST ($p=0.015$).

We found no significant difference in mean platelet count between NAFLD grade 1, grade 2 and grade 3. However, there is a rise in the platelet count in patients with grade 2 NAFLD when compared to grade 1 NAFLD and a fall in platelet count in grade 3 NAFLD when compared to grades 1 and 2. These findings correspond well with the data available, a number of studies show both positive or negative correlation between platelet count and the severity of NAFLD. Yoneda et al. (2011) in a study of 1048 patients with liver-biopsy-confirmed NAFLD found a linear decrease of the platelet count with increasing histological severity of hepatic fibrosis. However, the study by Garjani et al. (2015) has demonstrated that patients with mild fatty liver on ultrasonography had lower platelet counts than those with moderate and severe fatty liver. Another study by Saremi et al. (2017) has found a similar association between platelet count and grades of NAFLD. Both studies have concluded that no cut-off value of platelet count could reliably distinguish different grades of fatty liver. The reason for this discrepancy has been postulated. The negative correlation between platelet count and severity of NAFLD for liver fibrosis in some studies may be due to splenic sequestration of platelets, which might occur in patients with severe liver fibrosis and cirrhosis (Afdhal et al. 2008). It is also probable that the liver injury causes reduced platelet production in the bone marrow due to defective thrombopoietin (TPO) release. On the other hand, the positive correlation between platelet count and NAFLD may be due to the fact that platelet counts increase in response to inflammation, and hepatic

Table 3
Pearson's correlation between APRI score independent and dependent on grades of NAFLD and HOMA2-IR

	APRI		
	NAFLD grades	**Pearson correlation coefficient**	**p-value**
HOMA2 IR	–	0.9727	<0.001
HOMA2 IR	Grade 1	0.9628	<0.001
	Grade 2	0.9443	<0.001
	Grade 3	0.9869	<0.001

Abbreviations: APRI – aspartate aminotransferase platelet ratio index; HOMA2 – Homeostatic Model Assessment; IR – insulin resistance; NAFLD – nonalcoholic fatty liver disease.

inflammation is the channel through which hepatic steatosis leads to liver injury and fibrosis. Our study has shown a rise in the platelet count between grades 1 and 2 NAFLD, which correlates well with recent studies that have shown a rise between different stages of NAFLD. However, there is a fall in platelet count in patients with grade 3 NAFLD. This may be due to the increased severity of fibrosis which could only be examined on a liver biopsy.

In our study, a significant difference in mean HbA1C between grade 1, grade 2 and grade 3 NAFLD groups was found, which is in line with studies performed by Ghamar-Chehreh et al. (2012) and Bae et al. (2010). Based on the intergroup analysis, the mean HbA1C was significantly higher in NAFLD grade 3 compared to grades 1 and 2, which is well associated with the findings of Ghamar-Chehreh et al. (2012).

We found a significant difference in mean serum insulin levels between NAFLD grade 1, grade 2 and grade 3. The mean serum insulin values were significantly increased in the NAFLD grades 3 group compared to grades 1 and 2. Our results are similar to studies conducted by Jung et al. (2016) and Das et al. (2010).

A significant correlation between the NAFLD grades and APRI scores was demonstrated. We found a significant difference in the APRI values for three grades of NAFLD. The studies done by Yilmaz et al. (2011) and Sapmaz et al. (2016) have shown similar results.

We found a significant difference in mean HOMA2 IR between NAFLD grade 1, grade 2 and grade 3 as well as a significant difference in the intergroup comparisons of mean HOMA2 IR between all grades of NAFLD. Ghamar-Chehreh et al. (2012) and Aller et al. (2008) have shown similar results.

Finally, we found a significant positive correlation between the APRI score and HOMA2 IR and a strong positive correlation between the HOMA2 IR and APRI score for all three grades of NAFLD based on Pearson's correlation.

We could not find any study at the moment that has correlated APRI score directly with HOMA2 IR in patients with NAFLD and diabetes. Several studies have correlated APRI score and HOMA2 IR to grades of NAFLD individually, but none of them has correlated with the values of these two directly (APRI score vs. HOMA2). As established above, the APRI score is a good non-invasive test to evaluate liver fibrosis in NAFLD (Kruger et al. 2011; Lee et al. 2021). It is also well-established that HOMA2 IR is a strong indicator of hepatic fibrosis (Junior and Nonino-Borges 2012). So, we postulated that the APRI score can be correlated with HOMA2 IR in patients of NAFLD with diabetes. Our results show that there is a total positive correlation between APRI score and HOMA2 IR with different grades of NAFLD.

Study limitations

1) This was a cross-sectional study, which does not allow to make conclusions regarding the causality.

2) The small sample size is a limiting factor for the generalization of the results. Multicenter trials with a large population and a power analysis of the sample size are required in the future.

3) We used ultrasonography to diagnose and grade NAFLD. A liver biopsy is the gold standard for the diagnosis investigation and understanding of the extent of NAFLD. Newer, more sensitive and specific methods, involving transient elastography, might be used in future studies to improve the results of the present study.

4) All our patients were known cases of diabetes. The lack of a control group makes the results of this study less reliable and weaker for the establishment of causal relationships between independent and dependent variables.

5) We did not consider diabetic therapy in this study.

Conclusion

This study suggests that the APRI score can be confidently used to assess the degree of steatosis in patients with NAFLD and diabetes. It is suggested that the APRI score can also be used to assess the degree of IR and may provide important information for improving glycogenic control in such patients. Further studies are required to confirm our findings and better understand the underlying mechanisms.

Conflict of interest: *The authors declare no conflicts of interest.*

References

Afdhal N, McHutchison J, Brown R, Jacobson I, Manns M, Poordad F, Weksler B, Esteban R. Thrombocytopenia associated with chronic liver disease. J Hepatol 48, 1000–1007, 2008.

Aller R, de Luis, DA, Fernandez L. Influence of insulin resistance and adipokines in the grade of steatosis of nonalcoholic fatty liver disease. Dig Dis Sci 53, 1088–1092, 2008.
American Diabetes Association. Diabetes Care 43, S14–S31, 2020.
Bae JC, Cho YK, Lee WY, Seo H, Rhee EJ. Impact of nonalcoholic fatty liver disease on insulin resistance in relation to HbA1c levels in nondiabetic subjects. Am J Gastroenterol 105, 2389–2395, 2010.
Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, Grundy SM, Hobbs HH. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology 40, 1387–1395, 2004.
Das S, Singh SP, Parida PK, Mallik RN. Non-alcoholic fatty liver disease in subjects with type 2 diabetes mellitus and non-diabetics with special reference to insulin resistance and hepatic histopathological changes. Clin Res Rev 4, 226–229, 2010.
Forlani G, Giorda C, Manti R, Mazzella N, De Cosmo S, Rossi MC, Nicolucci A, Di Bartolo P, Ceriello A, Guida P; AMD-Annals Study Group. The burden of NAFLD and its characteristics in a nationwide population with type 2 diabetes. J Diabetes Res 2016, 2931985, 2016.
Garjani A, Safaeiyan A, Khoshbaten M. Association between platelet count as a noninvasive marker and ultrasonographic grading in patients with nonalcoholic fatty liver disease. Hepat Mon 15, e24449, 2015.
Ghamar-Chehreh ME, Khedmat H, Amini M, Taheri S. Predictive factors for ultrasonographic grading of nonalcoholic fatty liver disease. Hepat Mon 12, e6860, 2012.
Jimba S, Nakagami T, Takahashi M, Wakamatsu T, Hirota Y, Iwamoto Y, Wasada T. Prevalence of non-alcoholic fatty liver disease and its association with impaired glucose metabolism in Japanese adults. Diabet Med 22, 1141–1145, 2005.
Jung CH, Lee B, Choi DH, Jung SH, Kim BY. Association of the grade of non-alcoholic fatty liver disease and glycated albumin to glycated haemoglobin ratio in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract 125, 53–61, 2016.
Junior WS, Nonino-Borges CB. Clinical predictors of different grades of nonalcoholic fatty liver disease. Obes Surg 22, 248–252, 2012.
Kalra S, Vithalani M, Gulati G. Study of the prevalence of non-alcoholic fatty liver disease (NAFLD) in type 2 diabetes patients in India (SPRINT). J Assoc Physicians India 61, 448–453, 2013.
Kruger FC, Daniels CR, Kidd M, Swart G, Brundyn K, van Rensburg C, Kotze M. APRI: a simple bedside marker for advanced fibrosis that can avoid liver biopsy in patients with NAFLD/NASH. S Afr Med J 101, 477–480, 2011.
Lee J, Vali Y, Boursier J, Spijker R, Anstee QM, Bossuyt PM, Zafarmand MH. Prognostic accuracy of FIB-4, NAFLD fibrosis score and APRI for NAFLD-related events: A systematic review. Liver Int 41, 261–270, 2021.
Lin ZH, Xin YN, Dong QJ, Wang Q, Jiang XJ. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: An updated meta-analysis. Hepatology 53, 726–736, 2011.
Lopez-Velazquez JA, Silva-Vidal KV, Ponciano-Rodriguez G, Chavez-Tapia NC. The prevalence of non-alcoholic fatty liver disease in the Americas. Ann Hepatol 13, 166–178, 2014.
Machado MV, Cortez-Pinto H. Non-alcoholic fatty liver disease: what the clinician needs to know. World J Gastroenterol 20, 12956–12980, 2014.
Merriman RB, Ferrell LD, Patti MG, Weston SR, Pabst MS, Aouizerat BE, Bass NM. Correlation of paired liver biopsies in morbidly obese patients with suspected non-alcoholic fatty liver disease. Hepatology 44, 874–880, 2006.
Muzurovic E, Mikhailidis DP, Mantzoros C. Non-alcoholic fatty liver disease, insulin resistance, metabolic syndrome and their association with vascular risk. Metabolism 119, 154770, 2021.
Muzurovic E, Peng CC, Belanger MJ, Sanoudou D, Mikhailidis DP, Mantzoros CS. Nonalcoholic fatty liver disease and cardiovascular disease: a review of shared cardiometabolic risk factors. Hypertension 79, 1319–1326, 2022.
Ratziu V, Bellentani S, Cortez-Pinto H, Day C, Marchesini G. A position statement on NAFLD/NASH based on the EASL 2009 special conference. J Hepatol 53, 372–384, 2010.
Saadeh S, Younossi ZM, Remer EM, Gramlich T, Ong JP, Hurley M. The utility of radiological imaging in non-alcoholic fatty liver disease. Gastroenterology 123, 745–750, 2002.
Sapmaz F, Uzman M, Basyigit S. Steatosis grade is the most important risk factor for development of endothelial dysfunction in NAFLD. Medicine (Baltimore) 95, e3280, 2016.
Saremi Z, Rastgoo M, Mohammadifard M, Bijari B, Akbari E. Comparison of platelet number and function between nonalcoholic fatty liver disease and normal individuals. J Res Med Sci 22, 75, 2017.

Shah NADM, Kadla SA, Mir IA, Khan BA, Shah AI, Shiekh SA, Bhat KJ. Diagnostic accuracy of FIB-4, APRI, AST/ALT ratio for prediction of fibrosis in chronic hepatitis B and C patients. Nigerian Journal of Gastroenterology and Hepatology 9, 55–61, 2017.

Smith BW, Adams LA. Non-alcoholic fatty liver disease and diabetes mellitus: pathogenesis and treatment. Nat Rev Endocrinol 7, 456–465, 2011.

Suzuki A, Angulo P, Lymp J, St Sauver J, Muto A, Okada T, Lindor K. Chronological development of elevated aminotransferases in a nonalcoholic population. Hepatology 41, 64–71, 2005.

The University of Oxford. Diabetes trails unit. The Oxford centre of diabetes, Endocrinology and Metabolism https://www.dtu.ox.ac.uk/homacalculator/

Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, Lok AS. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 38, 518–526, 2003.

Xian YX, Weng JP, Xu F. MAFLD vs. NAFLD: shared features and potential changes in epidemiology, pathophysiology, diagnosis, and pharmacotherapy. Chin Med J (Engl) 134, 8–19, 2020.

Yilmaz Y, Yonal O, Kurt R, Bayrak M, Aktas B, Ozdogan O. Non-invasive assessment of liver fibrosis with the aspartate transaminase to platelet ratio index (APRI): Usefulness in patients with chronic liver disease: APRI in chronic liver disease. Hepat Mon 11, 103–106, 2011.

Yoneda M, Fujii H, Sumida Y. Platelet count for predicting fibrosis in nonalcoholic fatty liver disease. J Gastroenterol 46, 1300–1306, 2011.